```
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 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  JAN 17   Pre-1988 INPI data added to MARPAT
 NEWS  4  FEB 21   STN AnaVist, Version 1.1, lets you share your STN AnaVist
                   visualization results
 NEWS  5  FEB 22   The IPC thesaurus added to additional patent databases on STN
 NEWS  6  FEB 22   Updates in EPFULL; IPC 8 enhancements added
 NEWS  7  FEB 27   New STN AnaVist pricing effective March 1, 2006
 NEWS  8  MAR 03   Updates in PATDPA; addition of IPC 8 data without attributes
 NEWS  9  MAR 22   EMBASE is now updated on a daily basis
 NEWS 10  APR 03   New IPC 8 fields and IPC thesaurus added to PATDPAFULL
 NEWS 11  APR 03   Bibliographic data updates resume; new IPC 8 fields and IPC
                   thesaurus added in PCTFULL
 NEWS 12  APR 04   STN AnaVist $500 visualization usage credit offered
 NEWS 13  APR 12   LINSPEC, learning database for INSPEC, reloaded and enhanced
 NEWS 14  APR 12   Improved structure highlighting in FQHIT and QHIT display
                   in MARPAT
 NEWS 15  APR 12   Derwent World Patents Index to be reloaded and enhanced during
                   second quarter; strategies may be affected
 NEWS 16  MAY 10   CA/CAplus enhanced with 1900-1906 U.S. patent records
 NEWS 17  MAY 11   KOREAPAT updates resume
 NEWS 18  MAY 19   Derwent World Patents Index to be reloaded and enhanced
 NEWS 19  MAY 30   IPC 8 Rolled-up Core codes added to CA/CAplus and
                   USPATFULL/USPAT2
 NEWS 20  MAY 30   The F-Term thesaurus is now available in CA/CAplus
 NEWS 21  JUN 02   The first reclassification of IPC codes now complete in
                   INPADOC

 NEWS EXPRESS      FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
                   CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
                   AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
                   V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT
                   http://download.cas.org/express/v8.0-Discover/

 NEWS HOURS     STN Operating Hours Plus Help Desk Availability
 NEWS LOGIN     Welcome Banner and News Items
 NEWS IPC8      For general information regarding STN implementation of IPC 8
 NEWS X25       X.25 communication option no longer available after June 2006

Enter NEWS followed by the item number or name to see news on that
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FILE 'HOME' ENTERED AT 16:51:57 ON 12 JUN 2006

=> file reg
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COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         1.68       1.68

FILE 'REGISTRY' ENTERED AT 16:56:36 ON 12 JUN 2006
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DICTIONARY FILE UPDATES:  11 JUN 2006  HIGHEST RN 887399-72-6

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*                                                                   *
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* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                   *
*********************************************************************

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for details.

REGISTRY includes numerically searchable data for experimental and
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experimental property data in the original document.  For information
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http://www.cas.org/ONLINE/UG/regprops.html

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Uploading C:\Program Files\Stnexp\Queries\spermine.str

L1      STRUCTURE UPLOADED

=> sss l1 full
SSS IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s sss l1 full
FULL SEARCH INITIATED 16:56:54 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   296340 TO ITERATE

100.0% PROCESSED   296340 ITERATIONS                          7 ANSWERS
SEARCH TIME: 00.00.03

L2            7 SEA SSS FUL L1

=> file caplus biosis embase uspatful
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                       166.94     168.62

FILE 'CAPLUS' ENTERED AT 16:57:07 ON 12 JUN 2006
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FILE 'BIOSIS' ENTERED AT 16:57:07 ON 12 JUN 2006


FILE 'EMBASE' ENTERED AT 16:57:07 ON 12 JUN 2006

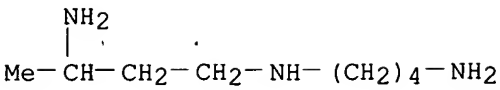

FILE 'USPATFULL' ENTERED AT 16:57:07 ON 12 JUN 2006


=> s l2
L3 17 L2

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4 17 DUP REM L3 (0 DUPLICATES REMOVED)

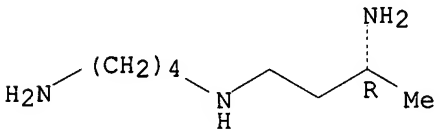
=> d ibib abs hitstr 1-17

L4 ANSWER 1 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:163695 CAPLUS
DOCUMENT NUMBER: 144:384807
TITLE: Guide Molecule-driven Stereospecific Degradation of α-Methylpolyamines by Polyamine Oxidase
AUTHOR(S): Jaervinen, Aki; Keinaenen, Tuomo A.; Grigorenko, Nikolay A.; Khomutov, Alex R.; Uimari, Anne; Vepsaelaeinen, Jouko; Naervaenen, Ale; Alhonen, Leena; Jaenne, Juhani
CORPORATE SOURCE: A. I. Virtanen Institute for Molecular Sciences and the Department of Chemistry, University of Kuopio, Kuopio, FI-70211, Finland
SOURCE: Journal of Biological Chemistry (2006), 281(8), 4589-4595
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB FAD-dependent polyamine oxidase (PAO; EC 1.5.3.11) is one of the key enzymes in the catabolism of polyamines spermidine and spermine. The natural substrates for the enzyme are N1-acetylspermidine, N1-acetylspermine, and N1,N12-diacetylspermine. Here we report that PAO, which normally metabolizes achiral substrates, oxidized (R)-isomer of 1-amino-8-acetamido-5-azanonane and N1-acetylspermidine as efficiently while (S)-1-amino-8-acetamido-5-azanonane was a much less preferred substrate. It has been shown that in the presence of certain aldehydes, the substrate specificity of PAO and the kinetics of the reaction are changed to favor spermine and spermidine as substrates. Therefore, we examined the effect of several aldehydes on the ability of PAO to oxidize different enantiomers of α-methylated polyamines. PAO supplemented with benzaldehyde predominantly catalyzed the cleavage of (R)-isomer of α-methylspermidine, whereas in the presence of pyridoxal the (S)-α-methylspermidine was preferred. PAO displayed the same stereospecificity with both singly and doubly α-methylated spermine derivs. when supplemented with the same aldehydes. Structurally related ketones proved to be ineffective. This is the first time that the stereospecificity of FAD-dependent oxidase has been successfully regulated by changing the supplementary aldehyde. These findings might facilitate the chemical regulation of stereospecificity of the enzymes.
IT **150333-68-9 878190-33-1 878190-34-2**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(guide mol.-driven stereospecific degradation of α-methylpolyamines by polyamine oxidase)
RN 150333-68-9 CAPLUS
CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



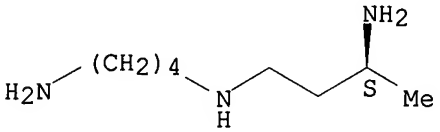
RN 878190-33-1 CAPLUS
CN 1,3-Butanediamine, N1-(4-aminobutyl)-, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 878190-34-2 CAPLUS
CN 1,3-Butanediamine, N1-(4-aminobutyl)-, (3S)- (9CI) (CA INDEX NAME)

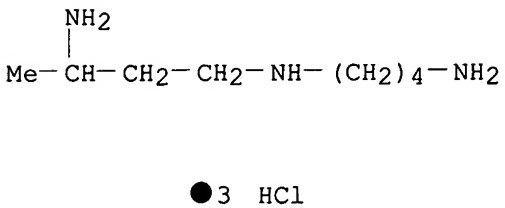
Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1306975 CAPLUS
DOCUMENT NUMBER: 144:212934
TITLE: α-Methyl Polyamines: Efficient Synthesis and Tolerance Studies in Vivo and in Vitro. First Evidence for Dormant Stereospecificity of Polyamine Oxidase
AUTHOR(S): Jaervinen, Aki J.; Cerrada-Gimenez, Marc; Grigorenko, Nikolay A.; Khomutov, Alex R.; Vepsaelaeinen, Jouko J.; Sinervirta, Riitta M.; Keinaenen, Tuomo A.; Alhonen, Leena I.; Jaenne, Juhani E.
CORPORATE SOURCE: Department of Biotechnology and Molecular Medicine, A.I. Virtanen Institute for Molecular Sciences, and Department of Chemistry, University of Kuopio, Kuopio, Finland
SOURCE: Journal of Medicinal Chemistry (2006), 49(1), 399-406
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 144:212934
AB Efficient syntheses of metabolically stable α-methylspermidine, α-methylspermine, and bis-α,α'-methylated spermine starting from Et 3-aminobutyrate are described. The biol. tolerance for these compds. was tested in wild-type mice and transgenic mice carrying the metallothionein promoter-driven spermidine/spermine N1-acetyltransferase gene (MT-SSAT). The efficient substitution of natural polyamines by their derivs. was confirmed in vivo with the rats harboring the same MT-SSAT transgene and in vitro with the immortalized fibroblasts derived from these animals. Enantiomers of previously unknown 1-amino-8-acetamido-5-azanonane dihydrochloride (I) were synthesized starting from enantiomerically pure (R)- and (S)-alaninols. The studies with recombinant human polyamine oxidase (PAO) showed that PAO (usually splits achiral substrates) strongly favors the (R)-isomer of I that demonstrates for the first time that the enzyme has hidden potency for stereospecificity.
IT **137945-92-7P**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological

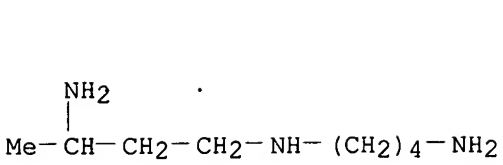
activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and tolerance studies in vivo and in vitro of spermine derivs.)
RN 137945-92-7 CAPLUS
CN 1,3-Butanediamine, N1-(4-aminobutyl)-, trihydrochloride (9CI) (CA INDEX NAME)



● 3 HCl

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

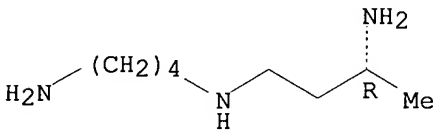
L4 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:149929 CAPLUS
DOCUMENT NUMBER: 142:385921
TITLE: Metabolic Stability of α-Methylated Polyamine Derivatives and Their Use as Substitutes for the Natural Polyamines
AUTHOR(S): Jaervinen, Aki; Grigorenko, Nikolay; Khomutov, Alex R.; Hyvoenen, Mervi T.; Uimari, Anne; Vepsaelaeinen, Jouko; Sinervirta, Riitta; Keinaenen, Tuomo A.; Vujcic, Slavoljub; Alhonen, Leena; Porter, Carl W.; Jaenne, Juhani
CORPORATE SOURCE: A. I. Virtanen Institute for Molecular Sciences, University of Kuopio, Kuopio, FIN-70211, Finland
SOURCE: Journal of Biological Chemistry (2005), 280(8), 6595-6601
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Metabolically stable polyamine derivs. may serve as useful surrogates for the natural polyamines in studies aimed to elucidate the functions of individual polyamines. Here we studied the metabolic stability of α-methylspermidine, α-methylspermine, and bis-α-methylspermine, which all have been reported to fulfill many of the putative physiol. functions of the natural polyamines. In vivo studies were performed with the transgenic rats overexpressing spermidine/spermine N1-acetyltransferase. α-Methylspermidine effectively accumulated in the liver and did not appear to undergo any further metabolism On the other hand, α-methylspermine was readily converted to α-methylspermidine and spermidine; similarly, bis-α-methylspermine was converted to α-methylspermidine to some extent, both conversions being inhibited by the polyamine oxidase inhibitor N1,N2-bis(2,3-butadienyl)-1,4-butanediamine. Furthermore, we used recombinant polyamine oxidase, spermidine/spermine N1-acetyltransferase, and the recently discovered spermine oxidase in the kinetic studies. In vitro studies confirmed that methylation did not protect spermine analogs from degradation, whereas the spermidine analog was stable. Both α-methylspermidine and bis-α-methylspermine overcame the proliferative block of early liver regeneration in transgenic rats and reversed the cytostasis induced by an inhibition of ornithine decarboxylase in cultured fetal fibroblasts.
IT **150333-68-9**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabolic stability of α-methylated polyamine derivs. and their use as substitutes for natural polyamines)
RN 150333-68-9 CAPLUS
CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:688737 CAPLUS
DOCUMENT NUMBER: 144:274446
TITLE: Synthesis of (R)- and (S)-isomers of 1-methylspermidine
AUTHOR(S): Grigorenko, Nikolay A.; Vepsalainen, Jouko; Jarvinen, Aki; Keinanen, Tuomo; Alhonen, Leena; Janne, Juhani; Khomutov, Alex R.
CORPORATE SOURCE: V.A. Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow, 119991, Russia
SOURCE: Mendeleev Communications (2005), (4), 142-143
CODEN: MENCEX; ISSN: 0959-9436
PUBLISHER: Russian Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Previously unknown (R)- and (S)-isomers of 1,8-diamino-5-azanonane were prepared starting from (R)- and (S)-2-aminopropanols.
IT **878133-12-1P 878133-13-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of (R)- and (S)-isomers of 1-methylspermidine)
RN 878133-12-1 CAPLUS
CN 1,3-Butanediamine, N1-(4-aminobutyl)-, trihydrochloride, (3R)- (9CI) (CA INDEX NAME)

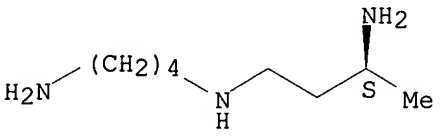
Absolute stereochemistry. Rotation (+).



●3 HCl

RN 878133-13-2 CAPLUS
CN 1,3-Butanediamine, N1-(4-aminobutyl)-, trihydrochloride, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



●3 HCl

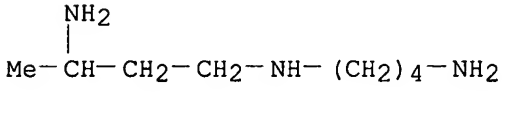
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:552063 CAPLUS
DOCUMENT NUMBER: 141:82364

TITLE: Spermidine analogs for prevention and treatment of pancreatitis and induction of liver regeneration
INVENTOR(S): Rasanen, Tiina-Liisa; Alhonen, Leena; Sinervirta, Riitta; Keinanen, Tuomo; Herzig, Karl-Heinz; Khomutov, Alex Radii; Vepsalainen, Jouko; Janne, Juhani
PATENT ASSIGNEE(S): Tiina-Liisa Rasanen, Finland; Leena Alhonen; Riitta Sinervirta; Tuomo Keinanen; Karl-Heinz Herzig; Alex Radii Khomutov; Jouko Vepsalainen; Juhani Janne
SOURCE: Jpn. Kokai Tokkyo Koho, 51 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| JP 2004189714 | A2 | 20040708 | JP 2003-33882 | | 20030212 |
| CA 2413720 | AA | 20040609 | CA 2002-2413720 | | 20021209 |
| CA 2452467 | AA | 20040609 | CA 2003-2452467 | | 20031209 |
| US 2004180968 | A1 | 20040916 | US 2003-731626 | | 20031209 |
| PRIORITY APPLN. INFO.: | | | US 2002-431958P | P | 20021209 |
| | | | CA 2002-2413720 | A | 20021209 |

OTHER SOURCE(S): MARPAT 141:82364
AB Spermidine analogs (I; R2R1N(CR3R4)aN(R10)(CR5R6)bN(R11)[(CR7R8)cN(R12)]nR 9 wherein a, b, c = 1-6; n = 0, 1; R1-R12 = H, alkyl), including 1-methylspermidine, are claimed for prevention and treatment of pancreatitis and induction of liver regeneration.
IT **150333-68-9**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(spermidine analogs for prevention and treatment of pancreatitis and induction of liver regeneration)
RN 150333-68-9 CAPLUS
CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 6 OF 17 USPATFULL on STN
ACCESSION NUMBER: 2004:233894 USPATFULL
TITLE: Methods for the treatment and prevention of pancreatitis and for induction of liver regeneration
INVENTOR(S): Rasanen, Tiina-Liisa, Syvanniemi, FINLAND
Alhonen, Leena, Vuorela, FINLAND
Sinervirta, Riitta, Syvanniemi, FINLAND
Keinanen, Tuomo, Kuopio, FINLAND
Herzig, Karl-Heinz, Kuopio, FINLAND
Khomutov, Alex Radii, Moscow, RUSSIAN FEDERATION
Vepsalainen, Jouko, Kuopio, FINLAND
Janne, Juhani, Vuorela, FINLAND

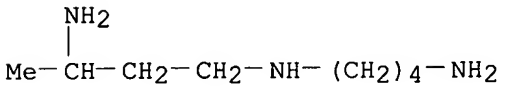
| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 2004180968 | A1 | 20040916 | |
| APPLICATION INFO.: | US 2003-731626 | A1 | 20031209 | (10) |

| | NUMBER | DATE | |
|---|---|---|---|
| PRIORITY INFORMATION: | US 2002-431958P | 20021209 | (60) |

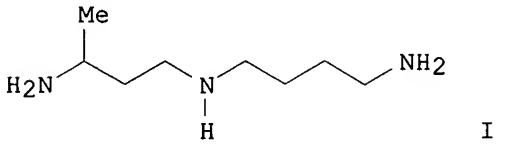
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WOODCOCK WASHBURN LLP, ONE LIBERTY PLACE, 46TH FLOOR, 1650 MARKET STREET, PHILADELPHIA, PA, 19103
NUMBER OF CLAIMS: 30

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Page(s)
LINE COUNT: 2039
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel methods for treating and preventing acute and/or chronic pancreatitis are described. Additionally, novel methods for inducing liver regeneration are described. The methods may comprise administering to a patient an effective amount of a metabolically stable analogue of spermidine and/or spermine. Preferred compounds for use in the methods may include 1-methylspermidine, 1-methylspermine and 1,12-dimethylspermine.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **150333-68-9**
(spermidine analogs for prevention and treatment of pancreatitis and induction of liver regeneration)
RN 150333-68-9 USPATFULL
CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:642169 CAPLUS
DOCUMENT NUMBER: 141:395701
TITLE: A New Synthesis of α-Methylspermidine
AUTHOR(S): Grigorenko, N. A.; Vepsalainen, J.; Jarvinen, A.; Keinanen, T. A.; Alhonen, L.; Janne, J.; Kritsyn, A. M.; Khomutov, A. R.
CORPORATE SOURCE: Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow, 119991, Russia
SOURCE: Russian Journal of Bioorganic Chemistry (Translation of Bioorganicheskaya Khimiya) (2004), 30(4), 396-399
CODEN: RJBCET; ISSN: 1068-1620
PUBLISHER: MAIK Nauka/Interperiodica Publishing
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:395701
GI



I

AB A five-step synthesis of α-methylspermidine (1,8-diamino-5-azanonane, I·3 HCl), the first polyamine analog preventing pathol. consequences of spermidine depletion in transgenic rats overproducing spermine/spermidine N1-acetyltransferase (no data), from Et 3-aminobutyrate was achieved in a high overall yield.
IT **137945-92-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(new synthesis of α-methylspermidine)
RN 137945-92-7 CAPLUS
CN 1,3-Butanediamine, N1-(4-aminobutyl)-, trihydrochloride (9CI) (CA INDEX NAME)

●3 HCl

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

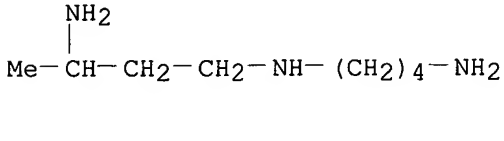
L4 ANSWER 8 OF 17 USPATFULL on STN
ACCESSION NUMBER: 2003:207355 USPATFULL
TITLE: Novel glycosidase inhibitors and their pharmacological uses, in particular for treating diabetes
INVENTOR(S): Aghajari, Nushin Banu Helene, Lyon, FRANCE
Robert, Xavier Guy, Lyon, FRANCE
Haser, Richard Michel, Lyon, FRANCE

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 2003143713 | A1 | 20030731 | |
| APPLICATION INFO.: | US 2002-168703 | A1 | 20021024 | (10) |
| | WO 2000-FR3600 | | 20001220 | |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | FR 1999-16409 | 19991223 |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: YOUNG & THOMPSON, 745 SOUTH 23RD STREET 2ND FLOOR, ARLINGTON, VA, 22202
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 959
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention concerns the use of a polyamine derivative or a polyamine for inhibiting the active site of glycosidase enzymes intervening in the transformation of polysaccharides into sugars, in particular into glucose, in a living organism.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **150333-68-9D**, α-amylase complexes
(polyamines and polyamine derivs. as glycosidase inhibitors and pharmacol. use, especially for treating diabetes)
RN 150333-68-9 USPATFULL
CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:489237 CAPLUS
DOCUMENT NUMBER: 135:71297
TITLE: Polyamines and polyamine derivatives as glycosidase inhibitors and their pharmacological uses, in particular for treating diabetes
INVENTOR(S): Aghajari, Nushin Banu Helene; Robert, Xavier Guy; Haser, Richard Michel
PATENT ASSIGNEE(S): Centre National de la Recherche Scientifique, Fr.
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001047528 | A2 | 20010705 | WO 2000-FR3600 | 20001220 |
| WO 2001047528 | A3 | 20020620 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| FR 2802817 | A1 | 20010629 | FR 1999-16409 | 19991223 |
| FR 2802817 | B1 | 20021011 | | |
| CA 2395305 | AA | 20010705 | CA 2000-2395305 | 20001220 |
| EP 1239863 | A2 | 20020918 | EP 2000-990069 | 20001220 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2003518501 | T2 | 20030610 | JP 2001-548121 | 20001220 |
| US 2003143713 | A1 | 20030731 | US 2002-168703 | 20021024 |

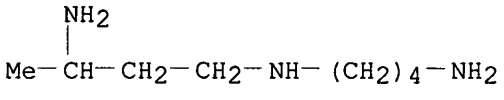
PRIORITY APPLN. INFO.: FR 1999-16409 A 19991223
WO 2000-FR3600 W 20001220

OTHER SOURCE(S): MARPAT 135:71297

AB The invention discloses the use of a polyamine or polyamine derivative for inhibiting the active site of glycosidases converting polysaccharides into sugars, in particular into glucose, in a living organism. The compds. of the invention are useful in the treatment of diabetes.

IT **150333-68-9D**, α-amylase complexes
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(polyamines and polyamine derivs. as glycosidase inhibitors and pharmacol. use, especially for treating diabetes)

RN 150333-68-9 CAPLUS
CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



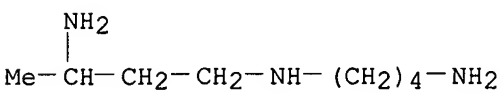
L4 ANSWER 10 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:252763 CAPLUS
DOCUMENT NUMBER: 135:73053
TITLE: Circular Dichroism and NMR Studies of Metabolically Stable α-Methylpolyamines: Spectral Comparison with Naturally Occurring Polyamines
AUTHOR(S): Varnado, Byron L.; Voci, Christopher J.; Meyer, Lynn M.; Coward, James K.
CORPORATE SOURCE: Departments of Medicinal Chemistry and Chemistry, The University of Michigan, Ann Arbor, MI, 48109-1055, USA
SOURCE: Bioorganic Chemistry (2000), 28(6), 395-408
CODEN: BOCMBM; ISSN: 0045-2068
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Three synthetic polyamine analogs, α-methylspermidine, α-methylspermine, and α,α'-dimethylspermine, were compared with their naturally occurring counterparts, spermidine and spermine, by two different spectral techniques. The interaction of polyamines with oligodeoxynucleotides was measured by CD in order to monitor the polyamine-induced conversion of right-handed B-DNA to the left-handed Z-form. The methylated analogs were shown to be equally

effective as the natural polyamines in inducing the B → Z transition. The pH dependence of the chemical shift of all carbon atoms in each of the five polyamines was measured by 13C-NMR spectroscopy. With the exception of expected changes in chemical shift due to the presence of the α-Me substituents, the chemical shifts and pH dependence of all carbon atoms in the three α-Me polyamines were similar to the corresponding naturally occurring polyamines. The combined data indicate that α-Me polyamines have phys. properties that are very similar to their natural counterparts. The two metabolically stable polyamine analogs, α-methylspermidine and α,α'-dimethylspermine, are therefore useful surrogates for spermidine and spermine in the study of numerous polyamine-mediated effects in mammalian cell cultures and can be used in such studies without the requirement for coadministration of amine oxidase inhibitors. (c) 2000 Academic Press.

IT **150333-68-9**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(metabolically stable Me polyamine analogs have phys. properties that are very similar to their natural counterparts)

RN 150333-68-9 CAPLUS
CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:570535 CAPLUS
DOCUMENT NUMBER: 121:170535
TITLE: Compositions and methods for inhibiting deoxyhypusine synthase and the growth of cells
INVENTOR(S): Jakus, Judit; Park, Myung Hee; Wolff, Edith C.; Folk, John E.
PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9415596 | A1 | 19940721 | WO 1993-US12310 | 19931216 |
| W: AU, CA, JP | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| US 5344846 | A | 19940906 | US 1992-998231 | 19921230 |
| AU 9458722 | A1 | 19940815 | AU 1994-58722 | 19931216 |
| PRIORITY APPLN. INFO.: | | | US 1992-998231 A | 19921230 |
| | | | WO 1993-US12310 W | 19931216 |

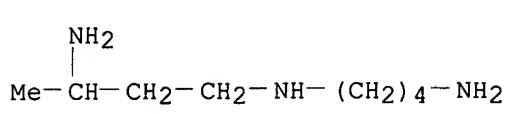
OTHER SOURCE(S): MARPAT 121:170535

AB Compns. and methods for the treatment of mammalian cells to inhibit cell growth, especially for inhibiting the proliferative cell growth associated with malignant and non-malignant disease, are provided. More particularly, a deoxyhypusine synthase inhibitor, typically, a mono- or bisguanyl diamine or polyamine, is administered to the cells. Also provided by this invention are diagnostic methods and kits for screening the cells of a patient to determine the effect of the deoxyhypusine synthase inhibitor on proliferation of the cells. Synthesis of compds. is given as is assay of enzyme inhibitory activity. Structure effects on activity is discussed.

IT **150333-68-9**
RL: PRP (Properties)
(activity of, against deoxyhypusine synthase of rat testis)

RN 150333-68-9 CAPLUS

CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



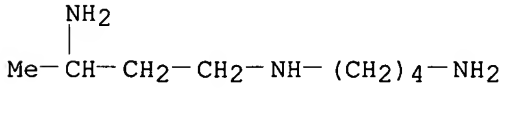
L4 ANSWER 12 OF 17 USPATFULL on STN
ACCESSION NUMBER: 94:77732 USPATFULL
TITLE: Compositions and methods for inhibiting deoxyhypusine synthase and the growth of cells
INVENTOR(S): Jakus, Judit, Silver Spring, MD, United States
Park, Myung H., Potomac, MD, United States
Wolff, Edith C., Bethesda, MD, United States
Folk, John E., Derwood, MD, United States
PATENT ASSIGNEE(S): The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 5344846 | | 19940906 | |
| APPLICATION INFO.: | US 1992-998231 | | 19921230 | (7) |

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: O'Sullivan, Peter
LEGAL REPRESENTATIVE: Townsend and Townsend Khourie and Crew
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Figure(s); 6 Drawing Page(s)
LINE COUNT: 1121
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compositions and methods for the treatment of mammalian cells to inhibit cell growth, especially for inhibiting the proliferative cell growth associated with malignant and non-malignant disease, are provided. More particularly, a deoxyhypusine synthase inhibitor, typically, a mono- or bisguanyl diamine or polyamine, is administered to the cells.

Also provided by this invention are diagnostic methods and kits for screening the cells of a patient to determine the effect of the deoxyhypusine synthase inhibitor on proliferation of the cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **150333-68-9**
(activity of, against deoxyhypusine synthase of rat testis)
RN 150333-68-9 USPATFULL
CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



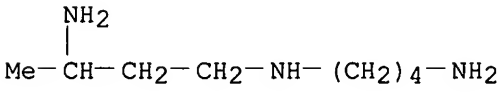
L4 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:627393 CAPLUS
DOCUMENT NUMBER: 121:227393
TITLE: The role of hypusine depletion in cytostasis induced by S-adenosyl-L-methionine decarboxylase inhibition: new evidence provided by 1-methylspermidine and 1,12-dimethylspermine
AUTHOR(S): Byers, Timothy L.; Lakanen, John R.; Coward, James K.; Pegg, Anthony E.
CORPORATE SOURCE: Department of Cell and Molecular Physiology, M.S. Hershey Medical Center, Hershey, PA, 17033, USA
SOURCE: Biochemical Journal (1994), 303(2), 363-8

CODEN: BIJOAK; ISSN: 0264-6021
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The abilities of the natural polyamines, spermidine and spermine, and of the synthetic analogs, 1-methylspermidine and 1,12-dimethylspermine, to reverse the effects of the S-adenosyl-L-methionine decarboxylase inhibitor 5'-{[(Z)-4-aminobut-2-enyl]methylamino}-5'-deoxyadenosine (AbeAdo) on L1210-cell growth were studied. L1210 cells were exposed to AbeAdo for 12 days to induce cytostasis and then exposed to spermidine, spermine, 1-methylspermidine or 1,12-dimethylspermine in the continued presence of AbeAdo. AbeAdo-induced cytostasis was overcome by the natural polyamines, spermidine and spermine. The cytostasis was also reversed by 1-methylspermidine. 1,12-Dimethylspermine had no effect on the AbeAdo-induced cytostasis of chronically treated cells, although it was active in permitting growth of cells treated with the ornithine decarboxylase inhibitor, α-difluoromethylornithine. The initial 12-day exposure to AbeAdo elevated intracellular putrescine levels, depleted intracellular spermidine and spermine, and resulted in the accumulation of unmodified eukaryotic translation initiation factor 5A (eIF-5A). Exposure of these cells to exogenous spermidine, which is the natural substrate for deoxyhypusine synthase, resulted in a decrease in the unmodified eIF-5A content. 1-Methylspermidine, which was found to be a substrate of deoxyhypusine synthase in vitro, also decreased the levels of unmodified eIF-5A in the AbeAdo-treated cells. Although spermine is not a substrate of deoxyhypusine synthase, spermine was converted into spermidine in the L1210 cells, and spermine addition to AbeAdo-treated cells resulted in the appearance of both intracellular spermine and spermidine and in the decrease in unmodified eIF-5A. Exogenous 1,12-dimethylspermine, which was not metabolized to spermine or to 1-methylspermidine and was not a substrate of deoxyhypusine synthase in vitro, did not decrease levels of unmodified eIF-5A. The finding that AbeAdo-induced cytostasis was only reversed by polyamines and polyamine analogs that result in the formation of hypusine or an analog in eIF-5A is consistent with the hypothesis (Byers, T. L., 1993) that AbeAdo-induced cytostasis is due to the depletion of the hypusine-containing form of eIF-5A, which is secondary to the depletion of spermidine by inhibition of S-adenosyl-L-methionine decarboxylase.

IT **150333-68-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(evidence provided by 1-methylspermidine and 1,12-dimethylspermine for the role of hypusine depletion in cytostasis induced by S-adenosyl-L-methionine decarboxylase inhibition)

RN 150333-68-9 CAPLUS
CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



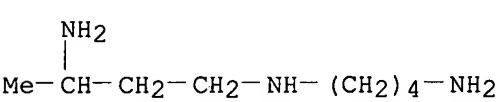
L4 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:576449 CAPLUS
DOCUMENT NUMBER: 119:176449
TITLE: Features of the spermidine-binding site of deoxyhypusine synthase as derived from inhibition studies. Effective inhibition by bis- and mono-guanylated diamines and polyamines
AUTHOR(S): Jakus, Judit; Wolff, Edith C.; Park, Myung Hee; Folk, J. E.
CORPORATE SOURCE: Lab. Cell. Dev. Oncol., Natl. Inst. Dent. Res., Bethesda, MD, 20892, USA
SOURCE: Journal of Biological Chemistry (1993), 268(18), 13151-9
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Several types of basic compds. structurally related to spermidine, one of the substrates for deoxyhypusine synthase, were tested as inhibitors of this enzyme. The results indicate that inhibitory compds. associate with the enzyme at the site of spermidine binding and must possess two charged primary amino or guanidino groups, or one of each. The efficiency of inhibition is related to the maximum possible distance between the primary amino groups and is adversely affected by substitutions on the secondary amino group or in the carbon chains of polyamines. The mono-guanyl derivs. are much more effective inhibitors than the parent amines or their bis-guanylated counterparts, N1-guanyl-1,7-diaminoheptane being the most effective compound with a Ki value of about 10 nM. Based on these observations a model is proposed for the spermidine-binding site of deoxyhypusine synthase. Studies with Chinese hamster ovary cells reveal a direct correlation between prevention of hypusine formation by several guanyldiamines and their in vitro inhibition of deoxyhypusine synthase. This evidence for disruption of the initial step in the post-translational maturation of eukaryotic initiation factor 5A provides a basis for the potential control of protein biosynthesis and cell proliferation.

IT **150333-68-9**
RL: BIOL (Biological study)
(deoxyhypusine synthase inhibition by, structure relation to)

RN 150333-68-9 CAPLUS

CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 15 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1992:105949 CAPLUS

DOCUMENT NUMBER: 116:105949

TITLE: α-Methyl polyamines: metabolically stable spermidine and spermine mimics capable of supporting growth in cells depleted of polyamines

AUTHOR(S): Lakanen, John R.; Coward, James K.; Pegg, Anthony E.

CORPORATE SOURCE: Dep. Chem., Univ. Michigan, Ann Arbor, MI, 48109-1055, USA

SOURCE: Journal of Medicinal Chemistry (1992), 35(4), 724-34
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal

LANGUAGE: English

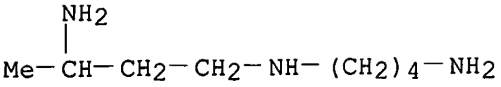
AB In order to assess the tolerance of the target enzyme spermine synthase for α-substituents on the aminopropyl moiety of the substrate spermidine, 1-methylspermidine (I) was synthesized. I is a poor substrate for spermine synthase and is not a substrate for spermidine N1-acetyltransferase, suggesting that α-methylated polyamines might be metabolically stable and therefore useful tools for studying polyamine effects in intact cells. On the basis of initial cellular results with I, 1-methylspermine (II) and 1,12-dimethylspermine (III) were also synthesized. When added to cells (L1210, SV-3T3, or HT29) depleted of both putrescine and spermidine by prior treatment with α-(difluoromethyl)ornithine (IV), these α-methylated polyamines were able to restore cell growth to that observed in the absence of IV. In accord with the enzyme data noted above, metabolic studies indicated a slow conversion of I to II, but no metabolism of III in these cells. It was concluded from these results that the α-methylated polyamines are able to substitute for the natural polyamines, spermidine and spermine in critical biochem. processes which involve polyamines for continued cell growth. In accord with the hypothesis, preliminary data indicate that I and III are as effective as spermidine and spermine, resp., in promoting the conversion of B-DNA to Z-DNA.

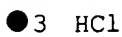
IT **137945-92-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 137945-92-7 CAPLUS

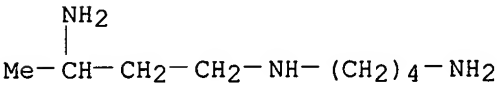
CN 1,3-Butanediamine, N1-(4-aminobutyl)-, trihydrochloride (9CI) (CA INDEX

NAME)

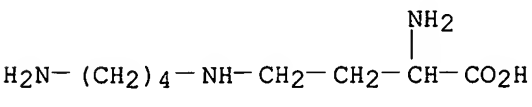




IT **150333-68-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as spermidine acetyltransferase substrate)
RN 150333-68-9 CAPLUS
CN 1,3-Butanediamine, N1-(4-aminobutyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1980:441626 CAPLUS
DOCUMENT NUMBER: 93:41626
TITLE: Coexistence of two pathways of spermidine biosynthesis in Lathyrus sativus seedlings
AUTHOR(S): Srivenugopal, K. S.; Adiga, P. R.
CORPORATE SOURCE: Biochem. Dep., Indian Inst. Sci., Bangalore, 560012, India
SOURCE: FEBS Letters (1980), 112(2), 260-4
CODEN: FEBLAL; ISSN: 0014-5793
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Evidence for the coexistence of both the classical S-adenosyl-L-methionine decarboxylase pathway and a recently proposed new route (aspartic β-semialdehyde forms a Schiff base with putrescine to be enzymically reduced by an NADPH-dependent step to yield "carboxyspermidine", which in turn undergoes a pyridoxal phosphate-dependent enzymic decarboxylation to give rise to spermidine) of spermidine biosynthesis in L. sativus seedlings is presented. The latter biosynthetic sequence is primarily restricted to spermidine synthesis.
IT **61715-48-8**
RL: BIOL (Biological study)
(as intermediate in spermidine biosynthetic pathway in Lathyrus sativus)
RN 61715-48-8 CAPLUS
CN Butanoic acid, 2-amino-4-[(4-aminobutyl)amino]- (9CI) (CA INDEX NAME)



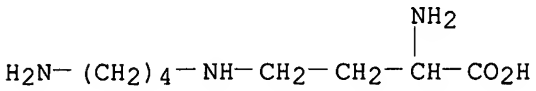
L4 ANSWER 17 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1977:52515 CAPLUS
DOCUMENT NUMBER: 86:52515
TITLE: A new pathway for the biosynthesis of spermidine
AUTHOR(S): Tait, George H.
CORPORATE SOURCE: Med. Sch., St. Mary's Hosp., London, UK
SOURCE: Biochemical Society Transactions (1976), 4(4), 610-12
CODEN: BCSTB5; ISSN: 0300-5127
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Studies of spermidine formation in Micrococcus denitrificans and Rhodopseudomonas spheroides using labeled precursors indicated the presence of an intermediate carboxyspermidine, H2N(CH2)4NH(CH2)2CH(NH2)CO2H (I), formed by reduction of a Schiff's base. In the presence of pyridoxal phosphate, I was decarboxylated to spermidine.

IT **61715-48-8**
RL: BIOL (Biological study)
(in spermidine formation, in Micrococcus denitrificans and Rhodopseudomonas sphaeroides)

RN 61715-48-8 CAPLUS

CN Butanoic acid, 2-amino-4-[(4-aminobutyl)amino]- (9CI) (CA INDEX NAME)



L7 ANSWER 3270 OF 3272 REGISTRY COPYRIGHT 2006 ACS on STN
RN 124-20-9 REGISTRY
ED Entered STN: 16 Nov 1984
CN 1,4-Butanediamine, N-(3-aminopropyl)- (8CI, 9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Spermidine (6CI)**
OTHER NAMES:
CN 1,5,10-Triazadecane
CN 1,8-Diamino-4-azaoctane
CN 4-Azaoctane-1,8-diamine
CN N-(3-Aminopropyl)-1,4-butanediamine
CN N-(3-Aminopropyl)-1,4-diaminobutane
CN N-(3-Aminopropyl)-4-aminobutylamine
CN N-(4-Aminobutyl)-1,3-diaminopropane
CN Spermidin
FS 3D CONCORD
MF C7 H19 N3
CI COM
LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DETHERM*, DRUGU, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, PIRA, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

9434 REFERENCES IN FILE CA (1907 TO DATE)
284 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
9446 REFERENCES IN FILE CAPLUS (1907 TO DATE)
86 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L8  ANSWER 402 OF 402  REGISTRY  COPYRIGHT 2006 ACS on STN
RN  71-44-3  REGISTRY
ED  Entered STN:  16 Nov 1984
CN  1,4-Butanediamine, N,N'-bis(3-aminopropyl)- (8CI, 9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN  **Spermine (6CI)**
OTHER NAMES:
CN  1,5,10,14-Tetraazatetradecane
CN  4,9-Diazadodecane-1,12-diamine
CN  Gerontine
CN  Musculamine
CN  N,N'-Bis(3-aminopropyl)-1,4-butanediamine
CN  N,N'-Bis(3-aminopropyl)-1,4-tetramethylenediamine
CN  Neuridine
CN  NSC 268508
CN  Spermin
FS  3D CONCORD
DR  115-04-8
MF  C10 H26 N4
CI  COM
LC  STN Files:  ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*,
    BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS,
    CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DRUGU,
    EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS,
    NAPRALERT, PIRA, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USPAT2,
    USPATFULL, VETU
      (*File contains numerically searchable property data)
    Other Sources:  EINECS**, NDSL**, TSCA**
      (**Enter CHEMLIST File for up-to-date regulatory information)



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

9218 REFERENCES IN FILE CA (1907 TO DATE)
 319 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
9230 REFERENCES IN FILE CAPLUS (1907 TO DATE)
 106 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>

L20 ANSWER 19 OF 225 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 81002150 EMBASE
DOCUMENT NUMBER: 1981002150
TITLE: The role of phospholipase A in acute **pancreatitis**
.
AUTHOR: Nevalainen T.J.
CORPORATE SOURCE: Lab. Electron Microscopy, Univ. Turku, 20520 Turku 52, Finland
SOURCE: Scandinavian Journal of Gastroenterology, (1980) Vol. 15, No. 6, pp. 641-650. .
CODEN: SJGRA4
COUNTRY: Norway
DOCUMENT TYPE: Journal
FILE SEGMENT: 048 Gastroenterology
029 Clinical Biochemistry
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Dec 1991
Last Updated on STN: 9 Dec 1991

AB Phospholipase A is a hydrolytic enzyme that splits one fatty acid off the phospholipid, e.g. from lecithin to form lysolecithin. Calcium ions and bile salt are essential for the enzymatic activity. The enzyme is synthesized by the pancreatic acinar cells, liberated to the pancreatic juice, and secreted in the duodenum for digestive purposes. It is synthetized and secreted under normal circumstances in enzymatically inactive as prophospholipase A, which is activated for trypsin. Phospholipase A is inhibited by e.g. zinc, EDTA, haloketones, structural analogs of the substrate, polyphloretin phosphate, antimalarial drugs of the chloroquine type, polyamines such as **spermine**, **spermidine**, and putrescine, local anesthetics related to procaine including chlorpromazine, and antibiotics including tetracycline and chloramphenicol. The pathogenetic role of phospholipase A in acute **pancreatitis** is supported by the observations that it and lysolecithin, when injected into the pancreatic duct of experimental animals, cause histologically similar changes - namely coagulation necrosis - in the gland as seen in cases of human acute **pancreatitis**. Increased phospholipase A and lysolecithin contents are found in pancreatic tissue in acute **pancreatitis**. Phospholipase A is elevated in the serum of patients with acute **pancreatitis**. Phospholipase A injected intravenously into experimental animals causes a decrease in arterial blood pressure. The respiratory distress syndrome associated with acute **pancreatitis** can be explained by the action of phospholipase A on the pulmonary surfactant, which consists of phospholipids. The enzyme may also be involved in the development of cerebral demyelination in acute **pancreatitis** and in the formation in ischemic pancreas of a myocardial depressant factor that plays an important role in various forms of circulatory shock. Specific therapy directed to the inhibition of phospholipase A in human and experimental acute **pancreatitis** has been successful with phospholipase A inhibitors sich as cytidine diphosphate choline, CaNa2-EDTA, xylocaine, procaine, and chlorpromazine. It is proposed in this review that inhibition and elimination of phospholipase A by enzyme inhibitors and immunochemical means and through detoxication methods such as hemodialysis and hemoperfusion should be investigated to find a novel and effectual treatment for acute **pancreatitis**.

L20 ANSWER 20 OF 225 USPATFULL on STN

L20 ANSWER 10 OF 225 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2006:211169 BIOSIS
DOCUMENT NUMBER: PREV200600212898
TITLE: Trypsin activation is followed by pancreatic polyamine depletion in severe sublehial acute **pancreatitis** model.
AUTHOR(S): Jin, Hailao; Lamsa, Teemu; Sand, Juhani; Raty, Sari; Herzig, Karl-Heinz; Alhonen, Leena; Nordback, Isto
SOURCE: Gastroenterology, (APR 2005) Vol. 128, No. 4, Suppl. 2, pp. A791.
Meeting Info.: Annual Meeting of the American-Gastroenterological-Association/Digestive-Disease-Week. Chicago, IL, USA. May 14 -19, 2005. Amer Gastroenterol Assoc.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Mar 2006
Last Updated on STN: 29 Mar 2006

AB Background: Previous findings have demonstrated that activation of polyamine catabolism in transgenic rats (over-expressing **spermidine/spermine** N'-acetyltransferase, SSAT) results in acute pancreatic inflammation, suggesting that depletion of polyamines (**spermine** and **spermidine**) may be one step in the evolution of acute **pancreatitis**. The purpose of this study was to explore this hypothesis in another model, and to study the timing of the changes in the polyamine metabolism in relation to trypsin activation. Methods: 36 rats (300g-350g) were divided into 2 groups ( **pancreatitis** group and sham group). In **pancreatitis** group 0.2 ml of 2.0% sodium taurodeoxycholate was infused into the pancreatic duct. In sham group the animals underwent laparotomy only. All animals were sacrificed and sampled under anesthesia at 3h, 24h and 48h. 6 rats served as 0 hour controls without operation. Serum amylase and pancreatic SSAT activities were measured. Pancreatic histology, water content and concentrations of **spermine**, **spermidine** and trypsin activation pepticle (TAP) were analysed, Results: In the **pancreatitis** group with hyperamylasemia, pancreatic edema, and **pancreatitis** histology SSAT was induced early, in association with trypsin, resulting in substantial decrease of both **spermine** and **spermidine** (Table). Pancreatic SSAT activity and TAP content correlated with each other (correlation coefficient 0.782, $P < 0.05$),[GRAPHICS]Conclusions: Another **pancreatitis** model (sodium taurocholate **pancreatitis**) is associated with the depletion of polyamines after induction of SSAT that occurs in association with the trypsin activation. Because polyamine depletion occurs between 3 arid 24 h after induction of **pancreatitis**, it may serve as a target for therapy in **pancreatitis**.

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 8 OF 225 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1978:613176 CAPLUS
DOCUMENT NUMBER: 89:213176
TITLE: Polyamine metabolism in ethionine-induced rat **pancreatitis**
AUTHOR(S): Yoshikawa, Daisuke
CORPORATE SOURCE: Dep. Intern. Med., Kobe Univ. Sch. Med., Kobe, Japan
SOURCE: Kobe Ika Daigaku Kiyo (1978), 37(4), 261-9
CODEN: KIDKA9; ISSN: 0375-927X
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB Changes in concentration of putrescine, **spermidine**, and **spermine** and in activity of ornithine decarboxylase were examined in pancreas of rat in which **pancreatitis** was induced by i.p. injection of ethionine in addition to protein deprivation from food for 5 days. Ornithine decarboxylase activity decreased to about 1/10 of preinjection value of 1st day of ethionine administration. Putrescine concentration increased continuously during ethionine injection, whereas **spermidine** and **spermine** decreased slowly to about 1/2 of preinjection value. After treatment for 5 days, ethionine administration was discontinued and a normal diet was given. Ornithine decarboxylase activity increased to 39-times of preinjection value 3.5 days after the discontinuation of the treatment, followed by a rapid decrease. Putrescine concentration decreased immediately after the disontinuation, whereas **spermidine** and **spermine** increased continuously and reached preinjection levels 10 days after discontinuation.

L20 ANSWER 7 OF 225 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:783211 CAPLUS
DOCUMENT NUMBER: 138:331376
TITLE: A Polyamine Analogue Prevents Acute **Pancreatitis** and Restores Early Liver Regeneration in Transgenic Rats with Activated Polyamine Catabolism
AUTHOR(S): Raesaenen, Tiina-Liisa; Alhonen, Leena; Sinervirta, Riitta; Keinaenen, Tuomo; Herzig, Karl-Heinz; Suppola, Suvikki; Khomutov, Alex R.; Vepsaelaeinen, Jouko; Jaenne, Juhani
CORPORATE SOURCE: A.I. Virtanen Institute for Molecular Sciences, University of Kuopio, Kuopio, FIN-70211, Finland
SOURCE: Journal of Biological Chemistry (2002), 277(42), 39867-39872
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We recently generated a transgenic rat model for acute **pancreatitis**, which was apparently caused by a massive depletion of pancreatic polyamines **spermidine** and **spermine** due to inducible activation of their catabolism (Alhonen, L., Parkkinen, J. J., Keinaenen, T., Sinervirta, R., Herzig, K. H., and Jaenne, J. (2000) Proc. Natl. Acad. Sci. U. S. A. 97, 8290-8295). When subjected to partial hepatectomy, these animals showed striking activation of polyamine catabolism at 24 h postoperatively with a profound decrease in hepatic **spermidine** and **spermine** pools and failure to initiate liver regeneration. Here we show that **pancreatitis** in this model could be totally prevented, as judged by histopathol. and plasma α-amylase activity, by administration of 1-methylspermidine, a metabolically stable analog of **spermidine**. Similarly, the analog, given prior to partial hepatectomy, restored early liver regeneration in the transgenic rats, as indicated by a dramatic increase in the number of proliferating cell nuclear antigen-pos. hepatocytes from about 1% to more than 40% in response to the drug. The present results suggest that the extremely high concentration of **spermidine** in the pancreas, in fact the highest in the mammalian body, may have a critical role in maintaining organ integrity. The failure to initiate liver regeneration in the absence of sufficient hepatic polyamine pools similarly indicates that polyamines are required for proper commencement of the regenerative process.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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     (FILE 'HOME' ENTERED AT 16:51:57 ON 12 JUN 2006)

     FILE 'REGISTRY' ENTERED AT 16:56:36 ON 12 JUN 2006
L1             STRUCTURE UPLOADED
L2               7 S SSS L1 FULL

     FILE 'CAPLUS, BIOSIS, EMBASE, USPATFULL' ENTERED AT 16:57:07 ON 12 JUN
     2006
L3              17 S L2
L4              17 DUP REM L3 (0 DUPLICATES REMOVED)

     FILE 'REGISTRY' ENTERED AT 16:58:57 ON 12 JUN 2006
L5             402 S SPERIDINE OR SPERMINE
L6            3538 S SPERMIDINE OR SPERMINE
L7            3272 S SPERMIDINE
L8             402 S SPERMINE

     FILE 'CAPLUS, BIOSIS, EMBASE, USPATFULL' ENTERED AT 17:00:30 ON 12 JUN
     2006
L9           45511 S SPERMINE OR SPERMIDINE
L10          46273 S L9 OR 71-44-3/RN OR 124-20-9/RN
L11          46273 S L10
L12         342976 S PANCREATITIS OR PANCREASE OR GREY TURNER SIGN OR CHOLELITHIAS
L13           1712 S L11 AND L12
L14           1684 S L11 AND (PANCREATITIS OR PANCREATIC OR GREY TURNER SIGN)
L15           1678 S L14 AND (SPERMIDINE OR SPERMIN OR SPERMINE)
L16           1358 S L14 AND (SPERMIDINE)
L17           1358 FOCUS L16 1-

=> s l11 and (pancreatitis or pancrease inflammation)
L18            236 L11 AND (PANCREATITIS OR PANCREASE INFLAMMATION)

=> dup rem l18
PROCESSING COMPLETED FOR L18
L19            225 DUP REM L18 (11 DUPLICATES REMOVED)

=> focus
PROCESSING COMPLETED FOR L19
L20            225 FOCUS L19 1-

=> s l11 and (pancreatitis)
L21            236 L11 AND (PANCREATITIS)

=> d ibib abs 1-30 l20

L20  ANSWER 1 OF 225  USPATFULL on STN
ACCESSION NUMBER:       2004:233894  USPATFULL
TITLE:                  Methods for the treatment and prevention of
                        pancreatitis and for induction of liver
                        regeneration
INVENTOR(S):            Rasanen, Tiina-Liisa, Syvanniemi, FINLAND
                        Alhonen, Leena, Vuorela, FINLAND
                        Sinervirta, Riitta, Syvanniemi, FINLAND
                        Keinanen, Tuomo, Kuopio, FINLAND
                        Herzig, Karl-Heinz, Kuopio, FINLAND
                        Khomutov, Alex Radii, Moscow, RUSSIAN FEDERATION
                        Vepsalainen, Jouko, Kuopio, FINLAND
                        Janne, Juhani, Vuorela, FINLAND

                             NUMBER       KIND    DATE
                        --------------- ------ --------
PATENT INFORMATION:     US 2004180968      A1   20040916
APPLICATION INFO.:      US 2003-731626     A1   20031209  (10)

                               NUMBER        DATE
                        ------------------ --------
PRIORITY INFORMATION:   US 2002-431958P    20021209 (60)
DOCUMENT TYPE:          Utility
```

FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WOODCOCK WASHBURN LLP, ONE LIBERTY PLACE, 46TH FLOOR, 1650 MARKET STREET, PHILADELPHIA, PA, 19103
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Page(s)
LINE COUNT: 2039
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel methods for treating and preventing acute and/or chronic **pancreatitis** are described. Additionally, novel methods for inducing liver regeneration are described. The methods may comprise administering to a patient an effective amount of a metabolically stable analogue of **spermidine** and/or **spermine**. Preferred compounds for use in the methods may include 1-methylspermidine, 1-methylspermine and 1,12-dimethylspermine.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L20 ANSWER 2 OF 225 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:195392 CAPLUS
DOCUMENT NUMBER: 143:303698
TITLE: Acute **pancreatitis** induced by activation of the polyamine catabolism in gene-modified mice and rats overexpressing **spermidine/spermine** N1-acetyltransferase
AUTHOR(S): Herzig, Karl-Heinz; Janne, Juhani; Alhonen, Leena
CORPORATE SOURCE: Department of Biotechnology and Molecular Medicine, A.I. Virtanen Institute for Molecular Sciences, University of Kuopio, Finland
SOURCE: Scandinavian Journal of Gastroenterology (2005), 40(1), 120-121
CODEN: SJGRA4; ISSN: 0036-5521
PUBLISHER: Taylor & Francis
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Premature intracellular activation of digestive zymogens is the initiating factor in the course of acute **pancreatitis**. In transgenic rats overexpressing **spermidine/spermine** N1-acetyltransferase (SSAT) gene under the control of an inducible mouse metallothionein I promoter, administration of zinc resulted in acute **pancreatitis** by depletion of **spermidine** and **spermine**. A sufficient pool of higher polyamine levels seems therefore essential to maintain pancreatic integrity. The induction of **pancreatitis** by activation of SSAT could be prevented by the administration of 1-methylspermidine, a metabolically stable analog of **spermidine**.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 3 OF 225 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:525360 CAPLUS
DOCUMENT NUMBER: 133:221079
TITLE: Activation of polyamine catabolism in transgenic rats induces acute **pancreatitis**
AUTHOR(S): Alhonen, Leena; Parkkinen, Jyrki J.; Keinanen, Tuomo; Sinervirta, Riitta; Herzig, Karl-Heinz; Janne, Juhani
CORPORATE SOURCE: A. I. Virtanen Institute for Molecular Sciences, University of Kuopio, Kuopio, FIN-70211, Finland
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2000), 97(15), 8290-8295
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Polyamines are required for optimal growth and function of cells. Regulation of their cellular homeostasis is therefore tightly controlled. The key regulatory enzyme for polyamine catabolism is the **spermidine/spermine** N1-acetyltransferase (SSAT). Depletion of cellular polyamines has been associated with inhibition of

growth and programmed cell death. To investigate the physiol. function SSAT, we generated a transgenic rat line overexpressing the SSAT gene under the control of the inducible mouse metallothionein I promoter. Administration of zinc resulted in a marked induction of pancreatic SSAT, overaccumulation of putrescine, and appearance of N1-acetylspermidine with extensive depletion of **spermidine** and **spermine** in transgenic animals. The activation of pancreatic polyamine catabolism resulted in acute **pancreatitis**. In nontransgenic animals, an equal dose of zinc did not affect pancreatic polyamine pools, nor did it induce **pancreatitis**. Acetylated polyamines, products of the SSAT-catalyzed reaction, are metabolized further by the polyamine oxidase (PAO) generating hydrogen peroxide, which might cause or contribute to the pancreatic inflammatory process. Administration of specific PAO inhibitor, MDL72527 [N1,N2-bis(2,3-butadienyl)-1,4-butanediamine], however, did not affect the histol. score of the **pancreatitis**. Induction of SSAT by the polyamine analog N1,N11-diethylnorspermine reduced pancreatic polyamines levels only moderately and without signs of organ inflammation. In contrast, the combination of N1,N11-diethylnorspermine with MDL72527 dramatically activated SSAT, causing profound depletion of pancreatic polyamines and acute **pancreatitis**. These results demonstrate that acute induction of SSAT leads to pancreatic inflammation, suggesting that sufficient pools of higher polyamine levels are essential to maintain pancreatic integrity. This inflammatory process is independent of the production of hydrogen peroxide by PAO.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 4 OF 225 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:320281 CAPLUS
DOCUMENT NUMBER: 144:429469
TITLE: Genetic manipulation of polyamine catabolism in rodents
AUTHOR(S): Janne, Juhani; Alhonen, Leena; Pietila, Marko; Keinanen, Tuomo A.; Uimari, Anne; Hyvonen, Mervi T.; Pirinen, Eija; Jarvinen, Aki
CORPORATE SOURCE: Department of Biotechnology and Molecular Medicine, A.I. Virtanen Institute for Molecular Sciences, University of Kuopio, Kuopio, FI-70211, Finland
SOURCE: Journal of Biochemistry (Tokyo, Japan) (2006), 139(2), 155-160
CODEN: JOBIAO; ISSN: 0021-924X
PUBLISHER: Japanese Biochemical Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Activation of polyamine catabolism through the overexpression of **spermidine/spermine** N1-acetyltransferase (SSAT) in transgenic rodents does not only lead to distorted tissue polyamine homeostasis, manifested as striking accumulation of putrescine, appearance N1-acetylspermidine and reduction of tissue **spermidine** and/or **spermine** pools, but likewise creates striking phenotypic changes. The latter include loss of hair, lipoatrophy and female infertility. Forced expression of SSAT modulates skin, prostate and intestinal carcinogenesis, induces acute **pancreatitis** and blocks early liver regeneration. Although many of these features are directly attributable to altered tissue polyamine pools, some of them are more likely related to the greatly accelerated flux of the polyamines caused by activated catabolism and compensatorily enhanced biosynthesis.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 5 OF 225 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:552063 CAPLUS
DOCUMENT NUMBER: 141:82364
TITLE: **Spermidine** analogs for prevention and treatment of **pancreatitis** and induction of liver regeneration
INVENTOR(S): Rasanen, Tiina-Liisa; Alhonen, Leena; Sinervirta, Riitta; Keinanen, Tuomo; Herzig, Karl-Heinz; Khomutov,

Alex Radii; Vepsalainen, Jouko; Janne, Juhani
PATENT ASSIGNEE(S): Tiina-Liisa Rasanen, Finland; Leena Alhonen; Riitta Sinervirta; Tuomo Keinanen; Karl-Heinz Herzig; Alex Radii Khomutov; Jouko Vepsalainen; Juhani Janne
SOURCE: Jpn. Kokai Tokkyo Koho, 51 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| JP 2004189714 | A2 | 20040708 | JP 2003-33882 | | 20030212 |
| CA 2413720 | AA | 20040609 | CA 2002-2413720 | | 20021209 |
| CA 2452467 | AA | 20040609 | CA 2003-2452467 | | 20031209 |
| US 2004180968 | A1 | 20040916 | US 2003-731626 | | 20031209 |
| PRIORITY APPLN. INFO.: | | | US 2002-431958P | P | 20021209 |
| | | | CA 2002-2413720 | A | 20021209 |

OTHER SOURCE(S): MARPAT 141:82364
AB **Spermidine** analogs (I; R2R1N(CR3R4)aN(R10)(CR5R6)bN(R11)[(CR7R8)cN(R12)]nR9 wherein a, b, c = 1-6; n = 0, 1; R1-R12 = H, alkyl), including 1-methylspermidine, are claimed for prevention and treatment of **pancreatitis** and induction of liver regeneration.

L20 ANSWER 6 OF 225 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:106729 CAPLUS
TITLE: Activated polyamine catabolism in acute **pancreatitis**: α-methylated polyamine analogues prevent trypsinogen activation and **pancreatitis**-associated mortality
AUTHOR(S): Hyvonen, Mervi T.; Herzig, Karl-Heinz; Sinervirta, Riitta; Albrecht, Elke; Nordback, Isto; Sand, Juhani; Keinanen, Tuomo A.; Vepsalainen, Jouko; Grigorenko, Nikolay; Khomutov, Alex R.; Kruger, Burkhard; Janne, Juhani; Alhonen, Leena
CORPORATE SOURCE: Department of Biotechnology and Molecular Medicine, A. I. Virtanen Institute for Molecular Sciences, University of Kuopio, Kuopio, Finland
SOURCE: American Journal of Pathology (2005), Volume Date 2006, 168(1), 115-122
CODEN: AJPAA4; ISSN: 0002-9440
PUBLISHER: American Society for Investigative Pathology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Polyamines are essential for normal cellular growth and function. Activation of polyamine catabolism in transgenic rats overexpressing **spermidine/spermine** N1-acetyltransferase, the key enzyme in polyamine catabolism, results in severe acute **pancreatitis**. Here, we investigated the role of polyamine catabolism in **pancreatitis** and studied the effect of polyamine analogs on the outcome of the disease. Polyamine depletion was associated with arginine- and caerulein-induced **pancreatitis** as well as with human acute necrotizing and chronic secondary **pancreatitis**. Substitution of depleted polyamine pools with methylspermidine partially prevented arginine-induced necrotizing **pancreatitis** whereas caerulein-induced edematous **pancreatitis** remained unaffected. Transgenic rats receiving methylated polyamine analogs after the induction of **pancreatitis** showed less pancreatic damage than the untreated rats. Most importantly, polyamine analogs dramatically rescued the animals from **pancreatitis**-associated mortality. Induction of **spermidine/spermine** N1-acetyltransferase in acinar cells isolated from transgenic rats resulted in increased trypsinogen activation. Pretreatment of acini with bismethylspermine prevented trypsinogen activation, indicating that premature proteolytic activation is one of the effects triggered by polyamine depletion. Our data suggest that activation of polyamine catabolism is a general pathway in the pathogenesis of acute **pancreatitis** and that exptl. disease can be ameliorated with stable polyamine analogs.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 7 OF 225 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:783211 CAPLUS
DOCUMENT NUMBER: 138:331376
TITLE: A Polyamine Analogue Prevents Acute **Pancreatitis** and Restores Early Liver Regeneration in Transgenic Rats with Activated Polyamine Catabolism
AUTHOR(S): Raesaenen, Tiina-Liisa; Alhonen, Leena; Sinervirta, Riitta; Keinaenen, Tuomo; Herzig, Karl-Heinz; Suppola, Suvikki; Khomutov, Alex R.; Vepsaelaeinen, Jouko; Jaenne, Juhani
CORPORATE SOURCE: A.I. Virtanen Institute for Molecular Sciences, University of Kuopio, Kuopio, FIN-70211, Finland
SOURCE: Journal of Biological Chemistry (2002), 277(42), 39867-39872
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We recently generated a transgenic rat model for acute **pancreatitis**, which was apparently caused by a massive depletion of pancreatic polyamines **spermidine** and **spermine** due to inducible activation of their catabolism (Alhonen, L., Parkkinen, J. J., Keinaenen, T., Sinervirta, R., Herzig, K. H., and Jaenne, J. (2000) Proc. Natl. Acad. Sci. U. S. A. 97, 8290-8295). When subjected to partial hepatectomy, these animals showed striking activation of polyamine catabolism at 24 h postoperatively with a profound decrease in hepatic **spermidine** and **spermine** pools and failure to initiate liver regeneration. Here we show that **pancreatitis** in this model could be totally prevented, as judged by histopathol. and plasma α-amylase activity, by administration of 1-methylspermidine, a metabolically stable analog of **spermidine**. Similarly, the analog, given prior to partial hepatectomy, restored early liver regeneration in the transgenic rats, as indicated by a dramatic increase in the number of proliferating cell nuclear antigen-pos. hepatocytes from about 1% to more than 40% in response to the drug. The present results suggest that the extremely high concentration of **spermidine** in the pancreas, in fact the highest in the mammalian body, may have a critical role in maintaining organ integrity. The failure to initiate liver regeneration in the absence of sufficient hepatic polyamine pools similarly indicates that polyamines are required for proper commencement of the regenerative process.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

# Pancreatitis



**Last Updated:** March 21, 2005

**Synonyms and related keywords:** acute **pancreatitis**, chronic **pancreatitis**, peripancreatic fat necrosis, hemorrhagic **pancreatitis**, necrotizing **pancreatitis**, pancreatic abscesses, acute respiratory distress syndrome, ARDS, acute renal failure, hemorrhage, hypote shock, epigastric pain, right upper quadrant pain, biliary colic, binge alcohol consumption, alcohol abuse, Grey Turner sign, Cullen si stone disease, cholelithiasis, choledocholithiasis, endoscopic retrograde cholangiopancreatography, ERCP, hypertriglyceridemia

## AUTHOR INFORMATION

Section 1 of 9



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Coauthor(s): **Samer S Deeba, MD**, Fellow, Department of Surgery, St Mary's Hospital, Imperial College, Lo

Editor(s): **Jerome FX Naradzay, MD, FACEP**, Medical Director of Emergency Services, Department of Em Medicine, Mesa View Regional Hospital; **Francisco Talavera, PharmD, PhD**, Senior Pharmacy Editor, eM **Eugene Hardin, MD, FACEP, FAAEM**, Chair and Associate Professor, Department of Emergency Medicin Charles R Drew University of Medicine and Science; Chair, Department of Emergency Medicine, Martin Lut King, Jr/Drew Medical Center; **John Halamka, MD**, Chief Information Officer, CareGroup Healthcare Syste Assistant Professor of Medicine, Department of Emergency Medicine, Beth Israel Deaconess Medical Cent Assistant Professor of Medicine, Harvard Medical School; and **William K Mallon, MD**, Program Director, In Training, Associate Professor, Department of Emergency Medicine, University of Southern California

Disclosure

## INTRODUCTION

Section 2 of 9 Back To

Author Information Introduction Clinical Differentials Workup Treatment Medication Follow-up Bibliography

**Background: Pancreatitis** is an inflammatory process in which pancreatic enzymes autodigest the gland.

The gland can sometimes heal without any impairment of function or any morphologic changes. This proces known as acute **pancreatitis**. It can recur intermittently, contributing to the functional and morphologic loss gland. Recurrent attacks are referred to as chronic **pancreatitis**. Both forms of **pancreatitis** are present in t with acute clinical findings.

**Pathophysiology:** Because the pancreas is located in the retroperitoneal space with no capsule, inflammat spread easily. In acute **pancreatitis**, parenchymal edema and peripancreatic fat necrosis occur first. This pr known as acute edematous **pancreatitis**.

When necrosis involves the parenchyma, accompanied by hemorrhage and dysfunction of the gland, the inflammation evolves into hemorrhagic or necrotizing **pancreatitis**.

Pseudocysts and pancreatic abscesses can result from necrotizing **pancreatitis** because of enzymes being off by granulation tissue (ie, pseudocyst formation) or bacterial seeding of pancreatic or peripancreatic tissu pancreatic abscess formation). An ultrasound or, preferably, a CT scan can be used detect both.

The inflammatory process can cause systemic effects because of the presence of cytokines, such as bradyl and phospholipase A. These cytokines may cause vasodilation, increase in vascular permeability, pain, and leukocyte accumulation in the vessel walls. Fat necrosis may cause hypocalcemia. Pancreatic B cell injury r to hyperglycemia.

**Frequency:**

- **In the US:** Annual incidence of acute **pancreatitis** is 19.5 per 100,000 population and chronic **pancre** 8.3 per 100,000 population per year.

**Mortality/Morbidity:**

- Although acute **pancreatitis** should be noted, chronic **pancreatitis** has a more severe presentation as episodes recur.
- Acute respiratory distress syndrome (ARDS), acute renal failure, cardiac depression, hemorrhage, and hypotensive shock all may be systemic manifestations of acute **pancreatitis** in its most severe form.

**Race:** Annual incidence of acute **pancreatitis** in Native American persons is 4 per 100,000 population, in w persons is 5.7 per 100,000 population, and in black persons is 20.7 per 100,000 population.

**Sex:** No predilection exists.

**Age:** The risk for African American persons aged 35-64 years is 10 times higher than for any other group. A American persons are at higher risk than white persons in that same age group.

## CLINICAL

Section 3 of 9 Back To

**History:**

- The main presentation of acute **pancreatitis** is epigastric pain or right upper quadrant pain radiating tc back
- Nausea and/or vomiting
- Fever
- Query the patient about recent surgeries and invasive procedures (ie, endoscopic retrograde cholangiopancreatography) or family history of hypertriglyceridemia.
- Patients frequently have a history of previous biliary colic and binge alcohol consumption, the major ca acute **pancreatitis**.

**Physical:**

- Tachycardia
- Tachypnea
- Hypotension
- Fever
- Abdominal tenderness, distension, guarding, and rigidity
- Mild jaundice
- Diminished or absent bowel sounds
- Because of contiguous spread of inflammation (effusion) from the pancreas, lung auscultation may rev basilar rales, especially in the left lung.
- Occasionally, in the extremities, muscular spasm may be noted secondary to hypocalcemia.
- Severe cases may have a Grey Turner sign (ie, bluish discoloration of the flanks) and Cullen sign (ie, l discoloration of the periumbilical area) caused by the retroperitoneal leak of blood from the pancreas i hemorrhagic **pancreatitis**.

**Causes:**

- The major causes are long-standing alcohol consumption and biliary stone disease.
    - In developed countries, the most common cause of acute **pancreatitis** is alcohol abuse.
        - On the cellular level, ethanol leads to intracellular accumulation of digestive enzymes and t premature activation and release.

- On the ductal level, ethanol increases the permeability of ductules, which allow enzymes tc the parenchyma, resulting in pancreatic damage.
- Ethanol increases the protein content of the pancreatic juice and decreases bicarbonate le trypsin inhibitor concentrations. This leads to the formation of protein plugs that block the pancreatic outflow and obstruction.

- Another major cause of acute **pancreatitis** is biliary stone disease (eg, cholelithiasis, choledocholithiasis). A biliary stone may lodge in the pancreatic duct or ampulla of Vater and ob the pancreatic duct, leading to extravasation of enzymes into the parenchyma.

- Minor causes of acute **pancreatitis**
  - Medications, including azathioprine, corticosteroids, sulfonamides, thiazides, furosemides, NSAI mercaptopurine, methyldopa, and tetracyclines
  - Endoscopic retrograde cholangiopancreatography (ERCP)
  - Hypertriglyceridemia (When the triglyceride (TG) level exceeds 1000 mg/U, an episode of **pancr** is more likely.)
  - Peptic ulcer disease
  - Abdominal or cardiopulmonary bypass surgery, which may insult the gland by ischemia
  - Trauma to the abdomen or back, resulting in sudden compression of the gland against the spine posteriorly
  - Carcinoma of the pancreas, which may lead to pancreatic outflow obstruction
  - Viral infections, including mumps, Coxsackievirus, cytomegalovirus (CMV), hepatitis virus, Epste virus (EBV), and rubella
  - Bacterial infections, such as mycoplasma
  - Intestinal parasites, such as ascaris, which can block the pancreatic outflow
  - Pancreas divisum
  - Scorpion and snake bites
- Vascular factors, such as ischemia or vasculitis

## DIFFERENTIALS

Section 4 of 9 Back To

Author Information Introduction Clinical Differentials Workup Treatment Medication Follow-up Bibliography

Aneurysm, Abdominal
Cholangitis
Cholecystitis and Biliary Colic
Cholelithiasis
Gastroenteritis

Hepatitis
Mesenteric Ischemia
Obstruction, Large Bowel
Obstruction, Small Bowel

**Other Problems to be Considered:**

Perforated viscus
Acute peritonitis
Choledocholithiasis
Macroamylasemia
Macrolipasemia
Intestinal obstruction
Pancreatic cancer
Malabsorption syndromes/processes

## WORKUP

Author Information Introduction Clinical Differentials Workup Treatment Medication Follow-up Bibliography

**Lab Studies:**

- A complete blood count (CBC) demonstrates leukocytosis (WBC >12000) with the differential being sh polymorphs.
- If blood transfusion is necessary, as in cases of hemorrhagic **pancreatitis**, obtain type and crossmatcl
- Measure blood glucose level because it may be elevated from B cell injury in the pancreas.
- Obtain measurements for BUN, creatine (Cr), and electrolytes (Na, K, Cl, $CO_2$, P, Mg); a great disturb balance is usually found, secondary to third spacing of fluids.
- Measure amylase levels, preferably the Amylase P, which is more specific to pancreatic pathology. Le than normal strongly suggest the diagnosis of acute **pancreatitis**
- Lipase levels also are elevated and remain high for 12 days. In patients with chronic **pancreatitis** (usu abuse), lipase may be elevated in the presence of a normal serum amylase level
- Perform liver function tests (eg, alkaline phosphatase, serum glutamic-pyruvic transaminase [SGPT], s transaminase [SGOT], G-GT) and bilirubin, particularly with biliary origin **pancreatitis**.

**Imaging Studies:**

- Perform a plain KUB (Kidneys, ureters, bladder) with the patient in the upright position to exclude visc the diaphragm). In cases with a recurrent episode of chronic **pancreatitis**, peripancreatic calcifications
- Ultrasound can be used as a screening test. If overlying gas shadows secondary to bowel distention a specific.
- CT scan is the most reliable imaging modality in the diagnosis of acute **pancreatitis**. The criteria for di

Balthazar and colleagues into 5 grades, as follows:

- Grade A - Normal pancreas
- Grade B - Focal or diffuse gland enlargement
- Grade C - Intrinsic gland abnormality recognized by haziness on the scan
- Grade D - Single ill-defined collection or phlegmon
- Grade E - Two or more ill-defined collections or the presence of gas in or nearby the pancreas

- The use of contrast material intravenously is yet to be proved detrimental on the microcirculation of the necrotizing **pancreatitis**.

**Other Tests:**

- Para-aminobenzoic acid test (ie, bentiromide [Chymex] test) for chronic **pancreatitis**

## TREATMENT

Author Information Introduction Clinical Differentials Workup Treatment Medication Follow-up Bibliography

**Emergency Department Care:** Most of the cases presenting to the ED are treated conservatively, and app such treatment.

- Fluid resuscitation
  - Monitor accurate intake/output and electrolyte balance of the patient.
  - Crystalloids are used, but other infusions, such as packed red blood cells (PRBCs), are occasior in the case of hemorrhagic **pancreatitis**.
  - Central lines and Swan-Ganz catheters are used in patients with severe fluid loss and very low b
- Patients should have nothing by mouth, and a nasogastric tube should be inserted to assure an empty system at rest.
- Begin parenteral nutrition if the prognosis is poor and if the patient is going to be kept in the hospital fc
- Analgesics are used to relieve pain. Meperidine is preferred over morphine because of the greater spa sphincter of Oddi.
- Antibiotics are used in severe cases associated with septic shock or when the CT scan indicates that a has evolved.
- Other conditions, such as biliary **pancreatitis** associated with cholangitis, also need antibiotic coverag are the ones secreted by the biliary system, such as ampicillin and third generation cephalosporins.
- Continuous oxygen saturation should be monitored by pulse oximetry and acidosis should be correcte pending respiratory failure develops, intubation should be performed.

- Perform CT-guided aspiration of necrotic areas, if necessary.
- An ERCP may be indicated for common duct stone removal.

**Consultations:** Consult a general surgeon in the following cases:

- For phlegmon of the pancreas, surgery can achieve drainage of any abscess or scooping of necrotic p followed by postoperative lavage of the pancreatic bed.
- In patients with hemorrhagic **pancreatitis**, surgery is indicated to achieve hemostasis, particularly bec eroded in acute **pancreatitis**.
- Patients who fail to improve despite optimal medical treatment or patients who push the Ranson score operating room. Surgery in these cases may lead to a better outcome or confirm a different diagnosis.
- In biliary **pancreatitis**, a sphincterotomy (ie, surgical emptying of the common bile duct) can relieve th cholecystectomy may be performed to clear the system from any source of biliary stones.



## MEDICATION

Author Information Introduction Clinical Differentials Workup Treatment Medication Follow-up Bibliography

The goal of pharmacotherapy is to relieve pain and minimize complications.

Drug Category: *Antibiotics* -- Used to cover the microorganisms that may grow in biliary **pancreatitis** an **pancreatitis**. The empiric antibiotic regimen usually is based on the premise that enteric anaerobic and aer microorganisms are often the cause of pancreatic infections. Once culture sensitivities are made, adjustmer can be done.

| | |
|---|---|
| **Drug Name** | Ceftriaxone (Rocephin) -- Third-generation cephalosporin with broa negative activity; lower efficacy against gram-positive organisms; hi resistant organisms. Arrests bacterial growth by binding to one or m proteins. |
| **Adult Dose** | 1-2 g IM/IV once or divided bid |
| **Pediatric Dose** | 50-75 mg/kg/d IM/IV divided q12h |
| **Contraindications** | Documented hypersensitivity |
| **Interactions** | Probenecid may increase levels; coadministration with ethacrynic a aminoglycosides may increase nephrotoxicity |
| **Pregnancy** | B - Usually safe but benefits must outweigh the risks. |
| **Precautions** | Adjust dose in renal impairment; caution in breastfeeding women ar |
| **Drug Name** | Ampicillin (Marcillin, Omnipen) -- Bactericidal activity against suscep Alternative to amoxicillin when unable to take medication orally. |
| **Adult Dose** | 250-500 IM/IV mg q6h |
| **Pediatric Dose** | 25-50 mg/kg/d IM/IV divided q6-8h |
| **Contraindications** | Documented hypersensitivity; viral mononucleosis |
| **Interactions** | Probenecid and disulfiram elevate levels; allopurinol decreases effe effects on ampicillin rash; may decrease effects of oral contraceptiv |
| **Pregnancy** | B - Usually safe but benefits must outweigh the risks. |
| **Precautions** | Adjust dose in renal failure; evaluate rash and differentiate from hyp |

Drug Category: *Analgesics* -- Pain control is essential to quality patient care. It ensures patient comfort, and has sedating properties, which are beneficial for patients who have sustained trauma or have painful le

| | |
|---|---|
| **Drug Name** | Meperidine (Demerol) -- Analgesic with multiple actions similar to th produce less constipation, smooth muscle spasm, and depression c similar analgesic doses of morphine. |
| **Adult Dose** | 15-35 mg/h IV; 50-150 mg IM q3-4h |
| **Pediatric Dose** | 1.1-1.8 mg/kg IM q3-4h |
| **Contraindications** | Documented hypersensitivity; MAOIs; upper airway obstruction or s depression; during labor when delivery of premature infant is anticip |
| **Interactions** | Monitor for increased respiratory and CNS depression with coadmir hydantoins may decrease effects; avoid with protease inhibitors |
| **Pregnancy** | C - Safety for use during pregnancy has not been established. |
| **Precautions** | Caution in head injuries because may increase respiratory depressi (use only if absolutely necessary); caution when using postoperative pulmonary disease (suppresses cough reflex; substantially increase aggravate or cause seizures because of tolerance, even if no prior h disorders; monitor closely for morphine-induced seizure activity if se |

**FOLLOW-UP**

Author Information Introduction Clinical Differentials Workup Treatment Medication Follow-up Bibliography

**Further Inpatient Care:**

- Transfer patients with Ranson scores of 0-2 to a hospital floor.

- Transfer patients with Ranson scores 3-5 to an intensive care unit.
- Transfer patients with Ranson scores higher than 5 to an intensive care unit with emergency surgery a
- Two other systems, the Acute Physiology and Chronic Health Evaluation (APACHE) and the Multiple ( have been used recently, but these are used more in an ICU setting.

**Further Outpatient Care:**

- The patient should be followed routinely with physical examination and amylase and lipase assays.

**Complications:**

- Infected pancreatic necrosis may result from seeding of bacteria into the inflammation.
- An acute pseudocyst is an effusion of pancreatic juice that is walled off by granulation tissue after an e
- Hemorrhage into the GI tract retroperitoneum or the peritoneal cavity is possible because of erosion of
- Intestinal obstruction or necrosis may occur.
- Common bile duct obstruction may be caused by a pancreatic abscess, pseudocyst, or biliary stone th
- An internal pancreatic fistula from pancreatic duct disruption or a leaking pancreatic pseudocyst may c

**Prognosis:**

- Ranson developed a series of different criteria for the severity of acute **pancreatitis**.
  - Present on admission
    - Older than 55 years
    - WBC higher than 16,000 per mcL
    - Blood glucose higher than 200 mg/dL
    - Serum lactate dehydrogenase (LDH) more than 350 IU/L
    - SGOT (ie, aspartate aminotransferase [AST]) greater than 250 IU/L
  - Developing during the first 48 hours
    - Hematocrit fall more than 10%
    - BUN increase more than 8 mg/dL
    - Serum calcium less than 8 mg/dL
    - Arterial oxygen saturation less than 60 mm Hg

- Base deficit higher than 4 mEq/L
- Estimated fluid sequestration higher than 600 mL

- A Ranson score of 0-2 has a minimal mortality rate.
- A Ranson score of 3-5 has a 10%-20% mortality rate.
- A Ranson score higher than 5 has a mortality rate of more than 50% and is associated with more syst

**Patient Education:**

- Educate patients about the disease and advise then to avoid alcohol in binge amounts and to discontii fatty meals and abdominal trauma.
- For excellent patient education resources, visit eMedicine's Liver, Gallbladder, and Pancreas Center. A education article, **Pancreatitis**.

## BIBLIOGRAPHY

Author Information Introduction Clinical Differentials Workup Treatment Medication Follow-up Bibliography


- Calleja GA, Barkin JS: Acute **pancreatitis**. Med Clin North Am 1993 Sep; 77(5): 1037-56[Medline].
- Moscati RM: Cholelithiasis, cholecystitis, and **pancreatitis**. Emerg Med Clin North Am 1996 Nov; 14(4
- Plock JA, Schmidt J, Anderson SE, et al: Contrast-enhanced computed tomography in acute **pancrea** worsen its course due to impaired microcirculation?. Langenbecks Arch Surg 2005 Feb 12;[Medline].
- Schwartz Gr, et al: Acute **pancreatitis**. In: Principles and Practice of Emergency Medicine. Vol 2. 199
- Steer ML: Classification and pathogenesis of **pancreatitis**. Surg Clin North Am 1989 Jun; 69(3): 467-8
- Taylor SL, Morgan DL, Denson KD, et al: A comparison of the Ranson, Glasgow, and APACHE II scor organ system score in predicting patient outcome in **pancreatitis**. Am J Surg 2005 Feb; 189(2): 219-2
- Trede M, Carter DC: Acute **pancreatitis**. In: Surgery of the Pancreas. 1993: 161-259.
- Werner J, Feuerbach S, Uhl W, Buchler MW: Management of acute **pancreatitis**: from surgery to inter 2005 Mar; 54(3): 426-36[Medline].